

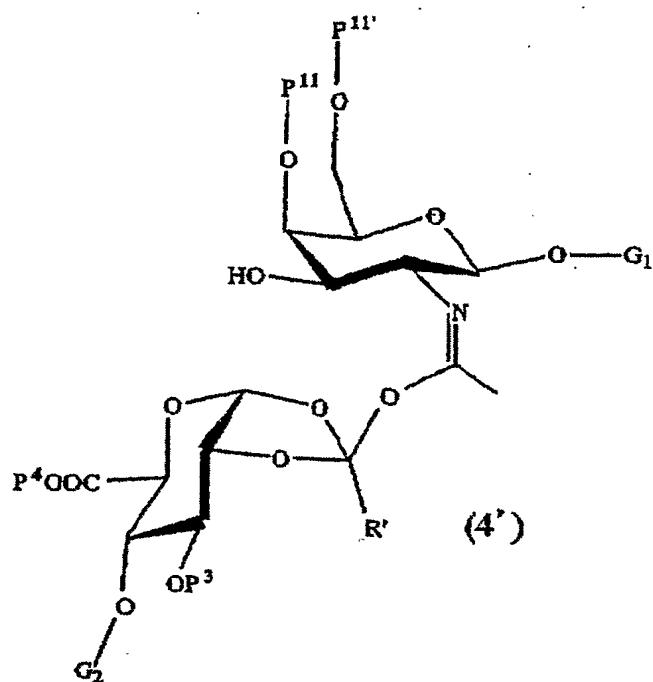
CLAIMS

1. A process for preparing an oligoglycosaminoglycan or a intermediate thereof, wherein the process comprises:

a step (A) of subjecting (A-1) a sugar donor having a glucuronic acid or iduronic acid derivative at the reducing end in which a leaving group is added to the reducing end hydroxyl group to be glycosylated and the other hydroxyl groups and the carboxyl groups are protected to the glycosylation reaction with (A-2) a sugar acceptor having a N-acylgalactosamine derivative at the non-reducing end in which the non-reducing end hydroxyl group to be glycosylated is free and the other hydroxyl groups are protected in the presence of (A-3) a Lewis acid as a promoter which is an activator for the leaving group of the sugar donor.

2. The process according to claim 1, wherein the intermediate is represented by the following general formula (4'):

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wherein R' is selected from the group consisting of an alkyl group, an alkenyl group, an aralkyl group and an aryl group;

$P^3$  is selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group and a silyl group optimally substituted with an alkyl group or an alkoxy group;

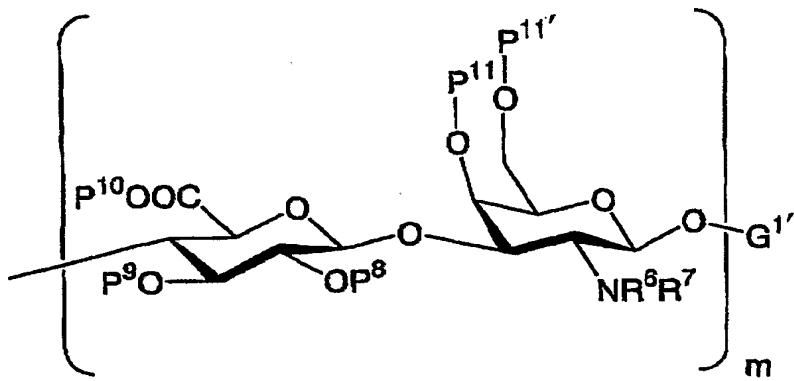
$P^4$  is selected from the group consisting of an alkyl group, an alkenyl group and an aralkyl group;

$P^{11}$  and  $P^{11'}$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, a silyl group optimally substituted with an alkyl group or an alkoxy group and an alkylidene group

and include one in which the two thereof are cross-linked; and

$G^1$  is selected from the group consisting of a hydrogen atom, an alkyl group, an aralkyl group, an alkenyl group, an aryl group and a compound represented by the following general formula (4-1):

(4-1)



wherein  $m$  is an integer of 0 to 4;

$R^6$  and  $R^7$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an acyl group and a phthaloyl group;

$P^8$  and  $P^9$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, an acyl group and a silyl group optimally substituted with an alkyl group or an alkoxy group;

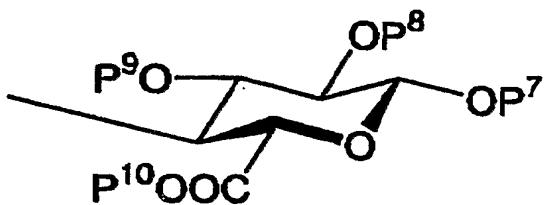
$P^{10}$  is selected from the group consisting of an alkyl group, an alkenyl group and an aralkyl group;

$P^{11}$  and  $P^{11}'$  are the same or independently

selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, a silyl group optimally substituted with an alkyl group or an alkoxy group and an alkylidene group and include one in which the two thereof are cross-linked; and

$G^1'$  is selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group and a compound represented by the following general formula (4-1'):

(4-1')



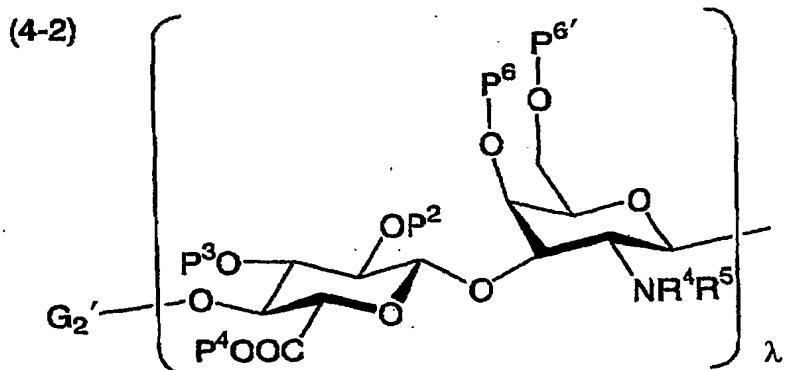
wherein  $P^7$  is selected from the group consisting of an alkyl group, an aralkyl group, an alkenyl group and an aryl group;

$P^8$  and  $P^9$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, an acyl group and a silyl group optimally substituted with an alkyl group or an alkoxy group; and

$P^{10}$  is selected from the group consisting of an alkyl group, an alkenyl group and an aralkyl group; and

$G^2$  is selected from the group consisting of a

hydrogen atom, an alkenyl group, an acyl group, an aralkyl group, a silyl group optinally substituted with an alkyl group or an alkoxy group and a compound represented by the following general formula (4-2):



wherein  $\lambda$  is an integer of 0 to 4;  
 $R^4$  and  $R^5$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an acyl group and a phthaloyl group;

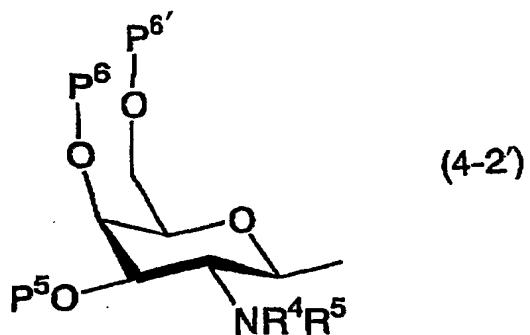
$P^2$  and  $P^3$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group and a silyl group optinally substituted with an alkyl group or an alkoxy group;

$P^4$  is selected from the group consisting of an alkyl group, an alkenyl group and an aralkyl group;

$P^6$  and  $P^{6'}$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, a silyl group optinally substituted with an alkyl group or an alkoxy group and an alkylidene group;

and

$G2'$  is selected from the group consisting of a hydrogen atom, an alkenyl group, an acyl group, an aralkyl group, a silyl group optimally substituted with an alkyl group or an alkoxy group and a compound represented by the following general formula (4-2'):

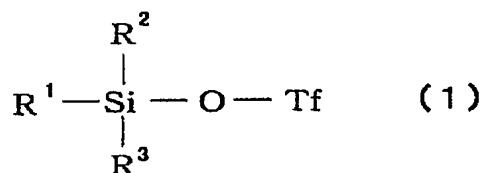


wherein  $R^4$  and  $R^5$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an acyl group and a phthaloyl group;

$P^5$  is selected from the group consisting of an alkenyl group, an acyl group, an aralkyl group and a silyl group optimally substituted with an alkyl group or an alkoxy group; and

$P^6$  and  $P^6'$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, a silyl group optimally substituted with an alkyl group or an alkoxy group and an alkylidene group.

3. The process according to claim 1 or 2, wherein the promoter is a compound represented by the following general formula (1):



wherein  $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  the same or independently represent a linear or branched alkyl group or an aromatic group unsubstituted or of which at least one of the hydrogen atoms are substituted, and Tf represents a trifluoromethanesulfonyl group.

4. The process according to any one of claims 1 to 3, wherein:

the sugar donor is a glucuronic acid or iduronic acid derivative in which a leaving group is added to the reducing end hydroxyl group to be glycosylated and the other hydroxyl groups and the carboxyl groups are protected, or an oligosaccharide derivative having as a basic constituent unit a basic disaccharide unit composed of a N-acylgalactosamine derivative and a glucuronic acid or iduronic acid derivative in which a leaving group is added to the reducing end hydroxyl group to be glycosylated and the other hydroxyl groups and the carboxyl groups are

protected; and

the sugar acceptor is a glucuronic acid or iduronic acid derivative in which the non-reducing end hydroxyl group to be glycosylated is free and the other hydroxyl groups and the carboxyl groups are protected, or an oligosaccharide derivative having as a basic constituent unit a N-acylgalactosamine derivative and a glucuronic acid or iduronic acid derivative in which the reducing end hydroxyl group to be glycosylated is free and the other hydroxyl groups and the carboxyl groups are protected.

5. The process according to any one of claims 1 to 4, further comprising the steps of:

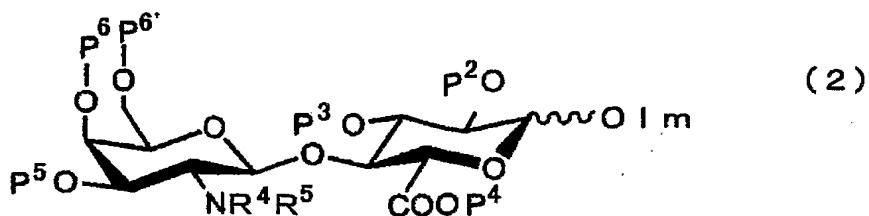
(B) eliminating one protecting group of the non-reducing end of the oligosaccharide derivative obtained in the above step (A), and

(C) subjecting the oligosaccharide derivative from which the one protecting group is eliminated to the glycosylation reaction with the sugar acceptor in the presence of the promoter; and

after the step (A), repeating these steps in an intended number of times within 1 to 8.

6. The process according to any one of claims 1 to 5, wherein:

the sugar donor is a chondroitin derivative represented by the following general formula (2):



wherein  $R^4$  and  $R^5$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an acyl group and a phthaloyl group;

$Im$  is an imidoyl optionally substituted with a halogen;

$P^2$  and  $P^3$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group and a silyl group optimally substituted with an alkyl group or an alkoxy group;

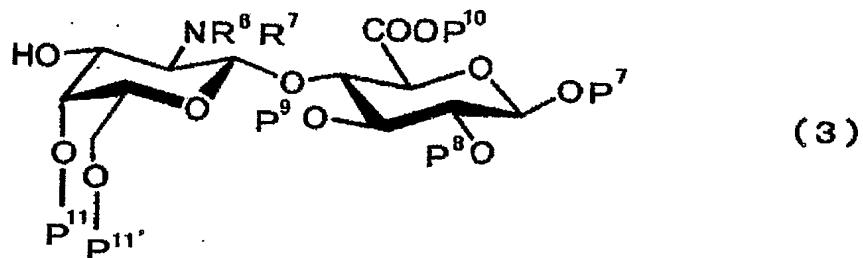
$P^4$  is selected from the group consisting of an alkyl group, an alkenyl group and an aralkyl group;

$P^5$  is selected from the group consisting of an alkenyl group, an acyl group, an aralkyl group and a silyl group optimally substituted with an alkyl group or an alkoxy group; and

$P^6$  and  $P^6'$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, a silyl group optimally substituted with an

alkyl group or an alkoxy group and an alkylidene group; and

the sugar acceptor is a reducing end glucuronic acid type chondroitin derivative represented by the following general formula (3):



wherein R<sup>6</sup> and R<sup>7</sup> are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an acyl group and phthaloyl group;

P<sup>7</sup> is selected from the group consisting of an alkyl group, an aralkyl group, an alkenyl group and an aryl group;

P<sup>8</sup> and P<sup>9</sup> are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, an acyl group and a silyl group optimally substituted with an alkyl group or an alkoxy group and an acyl group;

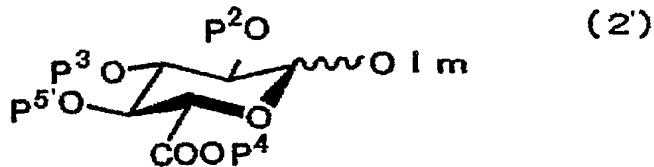
P<sup>10</sup> is selected from the group consisting of an alkyl group, an alkenyl group and an aralkyl group; and

P<sup>11</sup> and P<sup>11'</sup> are the same or independently

selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, a silyl group optimally substituted with an alkyl group or an alkoxy group and an alkylidene group and include one in which the two thereof are cross-linked.

7. The process according to any one of claims 1 to 5, wherein:

the sugar donor is a chondroitin derivative represented by the following general formula (2'):



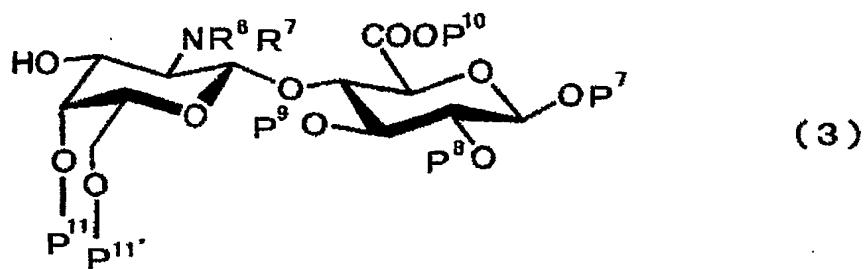
wherein Im is an imidoyl group optionally substituted with a halogen;

$P^2$  and  $P^3$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group and a silyl group optimally substituted with an alkyl group or an alkoxy group;

$P^4$  is selected from the group consisting of an alkyl group, an alkenyl group and an aralkyl group; and

$P^5'$  is selected from the group consisting of an alkenyl group, an acyl group, an aralkyl group and a silyl group optimally substituted with an alkyl group or an alkoxy group; and

the sugar acceptor used is a reducing end glucuronic acid type chondroitin derivative represented by the following general formula (3):



wherein  $R^6$  and  $R^7$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an acyl group and a phthaloyl group;

$P^7$  is selected from the group consisting of an alkyl group, an aralkyl group, an alkenyl group and an aryl group;

$P^8$  and  $P^9$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an aralkyl group, an aryl group, an acyl group and a silyl group optimally substituted with an alkyl group or an alkoxy group and an acyl group;

$P^{10}$  is selected from the group consisting of an alkyl group, an alkenyl group and an aralkyl group; and

$P^{11}$  and  $P^{11'}$  are the same or independently selected from the group consisting of a hydrogen atom,

an alkyl group, an alkenyl group, an aralkyl group, an aryl group, a silyl group optimally substituted with an alkyl group or an alkoxy group and an alkylidene group and include one in which the two thereof are cross-linked.

8. The process according to any one of claims 1 to 7, wherein the substituent at the 2nd position of the glucuronic acid or iduronic acid derivative in the sugar donor is protected by an acyl group which stabilizes an ortho ester.

9. The process according to any one of claims 3 to 8, wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently a hydrogen atom, or a linear or branched alkyl group.

10. The process according to any one of claims 1 to 9, wherein the promoter is trimethylsilyl trifluoromethanesulfonate (TMSOTf).

11. The process according to any one of claims 1 to 10, wherein the steps (B) and (C) are repeated in one to five times.

12. The process according to any one of claims 1 to 11, further comprising a step (D-1) in which all the protecting groups of the oligosaccharide derivative obtained in the step (A) or (C) are eliminated.

13. The process according to any one of claims 1 to 11, further comprising a step (D-2) in which all the protecting groups of the oligosaccharide derivative obtained in the step (A) or (C) are eliminated, and each N-acylgalactosamine are selectively sulfated at the 4th and 6th positions thereof.

14. The process according to claims 1 to 11 and 13, wherein the sugar donor is a compound represented by the general formula (2) or (2') and the sugar acceptor is the reducing end glucuronic acid type chondroitin derivative represented by the general formula (3);

wherein, if the oligosaccharide derivative obtained in the step (A) or (C) has an N-acylgalactosamine derivative at the non-reducing end, the hydroxyl groups at a position other than the 4th and 6th positions of the N-acylgalactosamine derivative are protected with a pivaloyl group;

the groups protecting the 4th and 6th positions of each N-acylgalactosamine derivative are eliminated; and

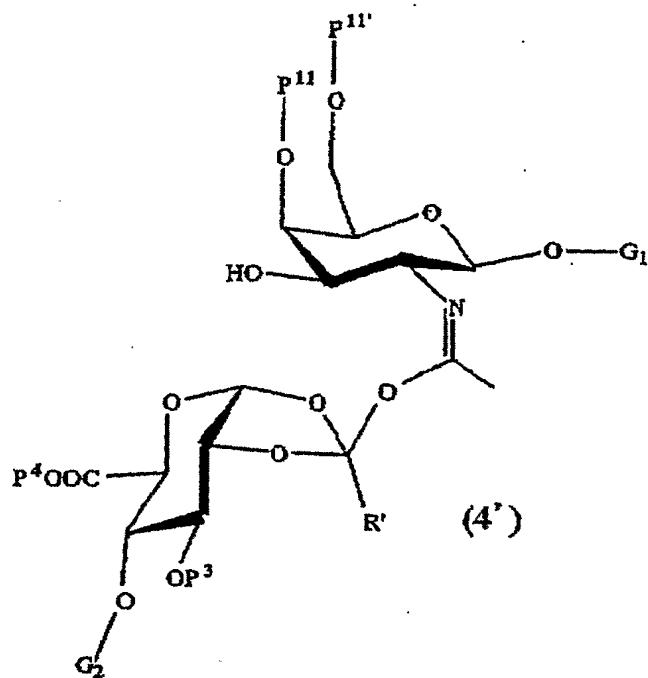
the deprotected oligosaccharide is sulfated to selectively sulfate the 4th and 6th positions of each N-acylgalactosamine.

15. The process according to claim 14, the protecting group is benzylidene, alkoxybenzylidene or

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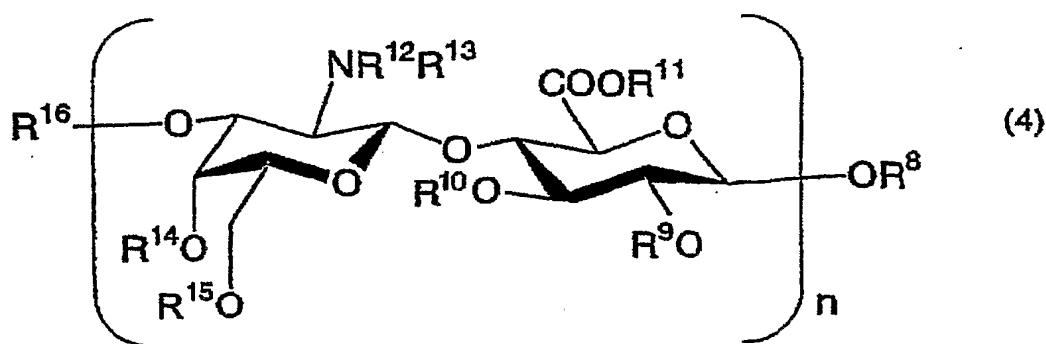
cyclohexylidene.

16. An oligoglycosaminoglycan intermediate compound represented by the general formula (4'):



wherein  $R'$ ,  $P^3$ ,  $P^4$ ,  $P^{11}$ ,  $P^{11'}$ ,  $G^1$  and  $G^2$  are the same as those defined in claim 2.

17. A reducing end glucuronic acid type oligochondroitin or a reducing end glucuronic acid type oligochondroitin sulfate, or a salt or derivative thereof represented by the following general formula (4):



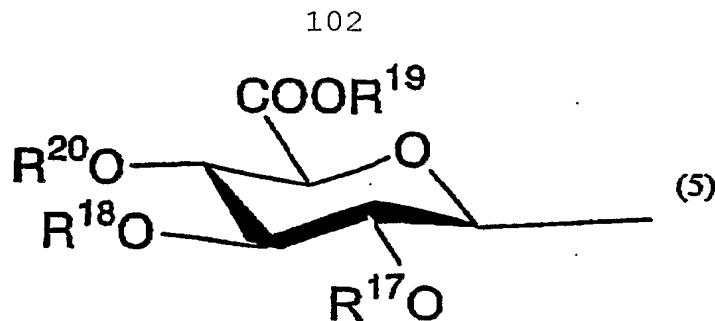
wherein n is an integer of 2 to 10;  
 $R^8$  represents a hydrogen atom or a protecting group;

$R^9$  to  $R^{11}$  are the same or independently represent a hydrogen atom or a protecting group;

$R^{12}$  and  $R^{13}$  are the same or independently selected from the group consisting of a hydrogen atom, an alkyl group, an alkenyl group, an acyl group and a phthaloyl group;

$R^{14}$  and  $R^{15}$  the same or independently represent a hydrogen atom, or a sulfate or phosphate group optionally substituted with any one selected from the group consisting of sodium, potassium, copper, calcium, iron, manganese, zinc, ammonium, barium and lithium; and;

$R^{16}$  represents a hydrogen atom, or a glucronic acid or iduronic acid derivative represented by the following general formula (5):



wherein  $R^{17}$ ,  $R^{18}$  and  $R^{19}$  represent the same or independently a hydrogen atom or a protecting group, or sodium, potassium, copper, calcium, iron, manganese, zinc, ammonium, barium or lithium; and  $R^{20}$  represents a hydrogen atom or a protecting group.

18. The reducing end glucuronic acid type oligochondroitin sulfate, or the salt or derivative thereof according to claim 17, wherein  $R^{14}$  and  $R^{15}$  are a sulfate group optionally substituted with one selected from the group consisting of sodium, potassium, copper, calcium, iron, manganese, zinc, ammonium, barium and lithium.

19. The reducing end glucuronic acid type oligochondroitin or a reducing end glucuronic acid type oligochondroitin sulfate, or the salt or derivative thereof according to claim 17 or 18, wherein n is 3 to 6.

20. A pharmaceutical composition comprising at least one selected from the group consisting of a reducing

end glucuronic acid type oligochondroitin and a reducing end glucuronic acid type oligochondroitin sulfate, and the salt and derivative thereof according to any one of claims 17 to 19 together with a pharmacologically acceptable carrier.

21. The pharmaceutical composition according to claim 20 for improving, treating or preventing a condition or diseases induced by a CD44 molecule.

22. The pharmaceutical composition according to claim 21 for treating an autoimmune disease, arthritis, an allergic disease or a cancer, or for modulating immunity or for inducing cell differentiation or cell apoptosis.

23. Use of a reducing end glucuronic acid type oligochondroitin or a reducing end glucuronic acid type oligochondroitin sulfate, or a salt or derivative thereof according to any one of claims 17 to 19 for the preparation of a pharmaceutical composition for improving, treating or preventing a condition or diseases induced by a CD44 molecule.

24. A method for improving, treating or preventing a condition or diseases induced by a CD44 molecule which comprise administering a reducing end glucuronic acid type oligochondroitin or a reducing end glucuronic acid

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type oligochondroitin sulfate, or a salt or derivative  
thereof according to any one of claims 17 to 19.